Study: Furlong et al. (2005)

Quality: High (8 points)					
D 1	E 1	O 2	C 2	A 1	B 1

Melissa Furlong, Caroline M Tanner, Samuel M Goldman, Grace S. Bhudhikanok, Aaron Blair, Anabel Chade, Kathleen Comyns, Jane A. Hoppin, Meike Kasten, Monica Korell, J William Langston, Connie Marras, Cheryl Meng, Marie Richards, G Webster Ross, David M Umbach, Dale P Sandler, and Freya Kamel. Protective glove use and hygiene habits modify the associations of specific pesticides with Parkinson's disease. *Environ Int. 2015 February; 0: 144–150. doi:10.1016/j.envint.2014.11.002.*

STUDY SUMMARY

Study Overview

The authors assessed whether use of gloves and workplace hygiene modified associations between pesticides and Parkinson's disease (PD) using data from the Farming and Movement Evaluation (FAME) Study, a nested case-control study within the Agricultural Health Study. FAME looked at use of protective gloves, other personal protective equipment (PPE), and hygiene practices, collecting questionnaire data from 69 cases and 237 controls. The analysis included interactions of gloves and hygiene with ever-use of pesticides for all pesticides with ≥ 5 exposed and unexposed cases and controls for each pesticide (paraquat, permethrin, rotenone, and trifluralin). The authors found evidence of a strong positive association between paraquat use and PD after adjusting for covariates and use of three other pesticides (OR 2.6 [95% CI 1.1 to 6.1). Protective glove use modified the associations of paraquat with PD: among protective glove users, there no evidence of a positive association between PD and pesticide use. In contrast, among non-users, they found evidence of a strong positive association between PD and paraquat use (OR 3.9 [95% CI 1.3, 11.7], interaction p=0.15). They also presented results for the other three pesticides. Although sample size in the FAME study limited the number of pesticides tested and the precision of the estimates, they conclude that protective glove use and hygiene practices appeared to be important modifiers of the association between pesticides and PD and may reduce risk of PD associated with certain pesticides.

Study Details

The Farming and Agricultural Movement Evaluation (FAME) study is a case-control study nested within the Agricultural Health Study (AHS). AHS is a prospective cohort study including 52,394 private pesticide applicators, mostly farmers, and 32,345 of their spouses. AHS subjects were recruited from 1993–1997 in Iowa and North Carolina.

Study Participants.
Cases: Suspect prevalent AHS PD cases were identified by self-report or from state mortality files. Case status was determined by the agreement of two movement disorder specialists.

Controls: Controls were randomly selected from the AHS cohort and frequency-matched to cases at a ratio of approximately three controls per case. The matching criteria included: age at enrollment into the AHS (<40, 40–49, 50–59, 60–64, 65–69, ≥70 years), sex, and state.

Exposure Measurement. Cases and controls in FAME completed structured telephone interviews between 2002 and 2008. The interviews collected information on demographics, lifestyle, medical history, a complete occupational history including details of all farm jobs, and information on PPE use and hygiene practices.

The complete occupational history was used to classify exposure (as "Never use" or "Ever use" (used one or more times before reference date)) to 31 different pesticides in each job held between age 14 and a reference date. The reference date for cases was age at PD diagnosis. The reference date for controls was the median age of PD diagnosis for cases in the corresponding age-, sex-and state- specific stratum.

Individuals who used pesticides during the late 1980s and early 1990s were asked questions about use of Personal Protective Equipment (PPE) and hygiene practices more or less than 50% of the time while mixing or applying pesticides. Three hygiene questions asked on whether respondents 1) usually bathed or showered after mixing or applying pesticides and before continuing with other farm activities, 2) changed their clothes after using pesticides, and 3) consistently washed concentrated pesticides off their skin after exposure.

Outcome Ascertainment. During home visits, neurologists examined living suspect cases and 5% of controls. Neurologist-trained technicians examined the remaining controls to ensure they did not have PD. Controls with evidence of Parkinsonism had a second in-home examination by a neurologist. Case status was determined by the agreement of two movement disorder specialists based on information from medical records, the in-home examination, and a videotaped movement evaluation conducted during the home visit.

Methods of Analysis. Unconditional logistic regression was used to evaluate the associations between PD and pesticides, PPE, and hygiene practices and obtained stratum-specific estimates from interaction models via the estimate statement in SAS PROC GENMOD.

For interaction analysis, they established a criterion that each case/control status × pesticide use × dichotomous glove variable needed to include ≥ 5 participants in order to test for an interaction. Four pesticides (trifluralin, permethrin, rotenone, and paraquat) met our criterion. One pesticide, 2,4-D, had large numbers of reported users but <5 cases who did not use the pesticide so they did not analyze 2,4-D.

Confounders Considered. Information on covariates was obtained from the FAME interviews. Frequency-matching variables were always included in analytic models. However, they used approximate age tertiles (40–57, 58–65, and 66–85) in the data analysis. Other potential confounders previously implicated in epidemiologic studies of PD that were considered included smoking (smoked>100 cigarettes before reference date), family history of PD (PD in any first-degree relative), and education (high school or less vs. some college/vocational school or higher). The final covariate set for all models included reference age (tertiles), sex, state, and smoking.

Effect Measure and Point Estimates.
The authors found evidence of a strong positive association between paraquat use and PD after adjusting for covariates and use of three other pesticides (OR 2.6 [95% CI 1.1 to 6.1]) based on

40 cases in the 222 subjects that never used paraquat and 22 cases in the 70 subjects that used paraquat at least once.

Protective glove use modified the associations of paraquat with PD: among protective glove users, there no evidence of a positive association between PD and pesticide use. In contrast, among non-users, they found evidence of a strong positive association between PD and paraquat use (OR 3.9 [95% CI 1.3, 11.7], interaction p=0.15).

They also presented results for the other three pesticides and on use of PPE and hygiene practices.

Strength and Limitations Discussed in the Paper

This study has some inherent limitations. The small sample size imposed limitations on which pesticides had enough data for analysis and when making inferences regarding effect modification. The authors used p<0.20 to maximize our ability to detect interactions at the risk of increasing false positives. Additionally, cell sizes are small and confidence intervals are fairly wide, particularly for trifluralin.

Aspects of study design may also contribute to bias. FAME relied on participants' recall to characterize exposures and protective habits (including glove use and hygiene habits), this could create bias if cases and controls differentially recall these behaviors. Cases may be less likely to accurately report glove use if they seek an explanation for their disease.

Reverse causation is also possible. For example, subjects with prodromal parkinsonian symptoms such as tremor may have been less willing or able to consistently wear protective gloves, which tend to be cumbersome and limit dexterity.

Another limitation is that pesticide use was evaluated over the lifetime up to a referent year, whereas PPE use was evaluated in the narrower time frame from the 1980s to the 1990s. PPE use and hygiene habits were evaluated generally, rather than for each specific pesticide. Thus, Inferences were based on the assumption that PPE and hygiene habits were constant across different pesticides.

EVALUATION

Using a case-control study design, Furlong et al. (2015) reported evidence of a strong positive association between self-reported use of paraquat and Parkinson's disease, in general and for the subpopulation that regularly wears gloves when mixing pesticides.

The authors provide a good discussion of the limitations, some of which are repeated below. The study had limitations related to its design, exposure assessment approach, and statistical analysis. With regard to study design, Furlong et al. relied on a case-control design. Although there is some unacknowledged uncertainty and possible bias associated with the selection of control subjects, this study selected the cases and controls from a prior prospective cohort, helping to minimize unintended differences between the populations that generated the cases and controls. The exposure assessment relied on self-reported use of paraquat (and other pesticides), PPE, and hygiene habits to ascertain exposure and covariate information. This reliance on self-report introduced uncertainty because it is not possible to attribute the increased odds of PD to paraquat exposure alone. Moreover, self-reported exposure assessment is likely to be subject to exposure misclassification (and associated bias or differential bias in the

parameter estimates) because study participants may be incorrectly recall previous pesticide usage. The need to rely on proxy respondents for 14 cases and 2 controls contributes additional uncertainty and possible bias. In the analysis, they fit many different but related models with no apparent criteria for selecting the best model or consideration of an adjustment for multiple testing. However, among the models they fit, one model included all selected covariates, four pesticides, and main effects for glove use and hygiene practices, allowing the evaluation of the relationship between paraquat exposure and PD adjusting for most of the possible covariates.

REFERENCES CITED

None.